Remarks

Applicants appreciate the Examiner's acknowledgement the claimed method is non-obvious in view of the following previously cited references, U.S. Patent No. 6,565,885 to Tarara *et al.*, U.S. Patent No. 5,21,961 to Mathiowitz *et al.*, and U.S. Patent No. 5,413,797 to Khan *et al.*

Priority Claim

Claim 16 as pending specifies that the microparticles have "a total surface area greater than about 0.5 m^2/mL". On page 2 of the Office Action, the Examiner erroneously indicates that the limitation "0.5 m^2/mL" is not supported by U.S.S.N. 09/433,486, filed November 4, 1999. This statement is incorrect.

To determine whether a claim in a later application is entitled to claim priority to an earlier application, one looks to the complete disclosure made in the earlier application. As noted by the Federal Circuit in *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1556, 37 U.S.P.Q.2d 1609 (Fed. Cir. 1996), "[a] later application is entitled to the earlier filing date for all common subject matter that is contained in the earlier application, whether the subject matter appears in the body of the specification or in the *claims* or drawings." (emphasis added)

The limitation "0.5 m^2/mL" was disclosed in parent application, U.S.S.N. 09/433,486, filed November 4, 1999 (now U.S. Patent No. 6,395,300) in claims 1 and 23 as originally filed (*see enclosed* pages 36 and 39 from U.S.S.N. 09/433,486, filed November 4, 1999). Therefore, claim 16 as pending is supported by the specification as originally filed and is entitled to its priority claim to U.S.S.N. 09/433,486, filed November 4, 1999. Applicants respectfully request correction of the Examiner's statement regarding the priority for the pending application.

Rejection Under 35 U.S.C. § 103

Claims 16-21 and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2001/0018072 to Unger *et al.* ("Unger"). Applicants respectfully traverse this rejection.

a. Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Case law makes clear that one "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

At page 2 of the Office Action, the Examiner requests evidence of "unexpected results" associated with Applicant's claimed method. However, such evidence is only useful to rebut a *prima facie* case of obviousness once one has been established. As discussed below, the Examiner has not established a *prima facie* case of obviousness for the claimed method.

b. The claimed method

Independent claim 16 and its dependent claims, claims 17-21, define methods for making a pharmaceutical composition that contains a porous matrix formed of at least one hydrophilic or hydrophobic excipient and microparticles of a drug. As specified in claim 16, the method requires the following steps:

(a) dissolving a drug in a volatile solvent to form a drug solution,

(b) combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution,

(c) incorporating at least one excipient into the emulsion, suspension, or second solution, wherein the excipient is selected from the group consisting of hydrophobic and hydrophilic excipients which enhance dissolution rate, which stabilize drug in amorphous form by preventing crystallization, and which stabilize drug in crystalline form by inhibiting crystal growth, and

(d) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient.

Independent claim 16 also specifies a number of physical properties of the composition produced by this method. The resulting composition contains microparticles of drug that have a mean diameter between about 0.1 and 5 μm and a total surface area greater than about 0.5 m^2/mL. Additionally the composition contains a dry porous matrix in a dry powder form, which has a TAP density less than or equal to 1.0 g/mL and a total surface area of greater than or equal to 0.2 m^2/g. As discussed in detail below, the claimed method is not obvious in view of Unger.

c. Unger

Unger does not disclose or suggest the claimed method. Unger describes a solid porous matrix containing a surfactant in combination with a bioactive agent (page 1, paragraph 0013).

The matrix may be prepared by (1) combining a surfactant and a therapeutic, together with a solvent, to form an emulsion containing random aggregates of the surfactant and the therapeutic, and (2) processing the emulsion by controlled drying, or controlled agitation and controlled drying to form the solid porous matrix (page 1, paragraph 0014).

Unger does not disclose or suggest element (a) of claim 16

Unger does not disclose or suggest dissolving a drug in a volatile solvent to form a drug solution

Unger clearly discloses that the active agent is **suspended** in the solvent (page 7, paragraph 0075). In contrast, claim 16 requires that the active agent is dissolved in a solvent (i.e., is soluble in a solvent) to form a solution. The Examiner asserts that since claim 34 recites the same classes of compounds as Unger, the drugs of the instant claims must also be marginally soluble. This assertion is incorrect. It is well-known in the art that whether a particular drug is soluble or not is dependent on the choice of solvent. One of ordinary skill in the art can readily determine which solvent is appropriate for a particular drug in order to form a solution. Unger's method requires a solvent in which the drug is marginally soluble (*i.e.*, to form a suspension). In contrast, the method defined by claim 16 requires a solvent in which the drug is soluble (*i.e.*, forms a solution).

Further, the Examiner mischaracterizes step (b) of claim 16. Step (b) of claim 16 refers to the addition of the volatile solid pore forming agent to the drug solution to form an emulsion, suspension, or second solution. The pore forming agent can be added as a solid to form a solution (if the pore forming agent is soluble in the solvent) or a suspension (if the pore forming agent is insoluble in the solvent). Alternatively, the pore forming agent can be added as a solution to the drug solution to form a second solution (if the two solvents are miscible in each

other) or an emulsion (if the two solvents are not miscible in each other). Thus, step (b) of claim 16 does not alter the fact that step (a) of claim 16 requires the use of a solvent in which the active agent is soluble to form a drug solution.

Unger does not disclose or suggest elements (b) and (d) of claim 16

Unger does not disclose or suggest adding a volatile solid pore forming agent to the drug solution and then removing the volatile pore forming agent

Unger describes the use of gases or gaseous precursors, which are **entrapped** within the matrix (page 20, paragraphs 0160 to page 22, paragraph 0175). Unger alleges that the entrapped gas provides the solid porous matrix with enhanced reflectivity. The gas and/or gaseous precursors are not "pore forming agents" nor are they removed from the matrix. Unger also describes the use of gaseous precursors as a solvent in the preparation of the solid matrix (page 20, paragraph 0161). In contrast, the claimed method requires the addition of a volatile solid pore forming agent, which is removed and upon removal, forms a porous matrix.

Volatile Solid Pore Forming Agents are a subset of Pore Forming Agents

Claim 16 requires a **volatile** solid pore forming agent. "Volatile" agents are agents that change readily from a solid or liquid to a vapor (*see* the attached definition from www.wordnet.princeton.edu). The compounds are typically evaporated using added heat and/or vacuum (page 20, lines 22-24 of the specification).

The Examiner cites several references which she alleges disclose volatile pore forming agents. U.S. Publication No. 20050283229 describes pore forming agents that are dissolved or eroded away by a fluid, such as a solvent or a bodily fluids (paragraph 0085). U.S. Patent No. 5,595,762 discloses that the pore forming agent is not removed from the compositions prior to

introduction into the body and is removed by dissipation into the surrounding tissue and/or bodily fluids (*see* col. 2, lines 57-62).

U.S. Patent No. 5,632,727 describes a composition containing a pore forming agent in which the agent diffuses out of the film and into the surrounding tissue (*see* col. 2, lines 61-67).

U.S. Patent No. 5,660,849 describes the use of a pore forming agent which is water soluble and dissipates from the matrix into the surrounding bodily fluids (*see* col. 7, lines 46-50).

U.S. Patent No. 5,681,873 describes agents that can be used to form pores *in situ* (*see* col. 3, lines 20-22).

U.S. Patent No. 5,906,826 describes compositions that optionally contain a soluble or insoluble pore forming agent that dissipates from the matrix into the surrounding bodily fluids (col. 9, lines 41-52).

All of the references cited by the Examiner disclose agents that form pores by dissipating out of the composition *in situ* into the surrounding tissues or bodily fluids; they are not volatilized as required by the claims. The Examiner specifically characterizes "polyethylene glycol", "sodium chloride", "starch", and "carboxymethyl cellulose", which are described in the references cited by the Examiner, as "volatile pore forming agents". Sodium chloride has a melting point of 800°C and a boiling point of 1,465°C (*see* the Material Safety Data Sheet for salt, a copy of which is enclosed). Starch decomposes at 250°C, which is before its melting point (*see* the Material Safety Data Sheet for starch, a copy of which is enclosed). Thus, these materials do not evaporate readily at relatively low temperatures and pressures; i.e., they are **not** volatile. Further, the pore forming agents of the present claims are removed prior to introducing the composition into the body; not *in situ* as required by the references cited by the Examiner.

Contrary to the Examiner's assertion, any agent that is listed in any prior art reference as a "pore forming agent" does not necessarily meet the limitations of claim 16.

Unger's Example 1 does not meet the limitations of Claim 16

The Examiner points to Example 1 in Unger to support of her obviousness rejection. Example 1 describes mixing dexamethasone and polyethylene glycol (PEG) to form a mixture and dissolving the mixture in methanol. The methanol is removed under vacuum to form a dry film. None of these materials is a volatile solid pore forming agent. Therefore, Example 1 does not describe adding a volatile solid pore forming agent to a drug solution to form an emulsion, suspension, or second solution as required by claim 16.

Unger does not disclose or suggest microparticles with the properties required by claim 16

Claim 16 specifies the properties of the compositions formed using the claimed method. Unger does not disclose or suggest that the microparticles formed using Unger's process have these properties. Further, Unger provides no suggestion or motivation to modify its method to produce particles with the properties specified by claim 16.

One or ordinary skill in the art would not be motivated to modify Unger to arrive at the claimed methods

In order to establish a *prima facie* case of obviousness, the references(s) must disclose or suggest each and every element of the claimed method. As noted above, Unger does not provide the necessary suggestion, teaching or motivation to practice the claimed method, as Applicants have done. For example, Unger does not disclose or suggest adding a volatile solid pore forming agent to a drug solution to form an emulsion, suspension or second solution, and removing the solid pore forming agent to form a porous matrix, nor does Unger suggest modifications to its

own method to arrive at the claimed method. Further, Unger does not disclose or suggest that the microparticles formed using its process have the properties required by claim 16. Therefore claims 16-21 are not obvious in view of Unger.

Double Patenting Rejection

Claims 16-21 and 34 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11-14 of U.S. Patent No. 6,932,983 to Bernstein *et al.* Without making any admissions and solely for the purpose of facilitating prosecution, the applicants submit a Terminal Disclaimer to overcome the double patenting rejection.

Allowance of claims 16-21 and 34 is respectfully solicited.

Respectfully submitted,

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